Elimination

Introduction

Elimination is defined as how much of a drug is **removed from the body**. It doesn't mean how fast the effect wears off. The effect of a drug is reduced both by metabolism and by excretion. In this lesson we focus on **elimination**. Think about how stuff—anything—comes out of you. Breath, sweat, stool, and urine. Those are the routes of elimination. And as discussed in Nephrology, most of the excreting comes from the kidneys. Think of it this way (though not entirely true, it helped me keep things straight): the **liver metabolizes**, the **kidney eliminates**.

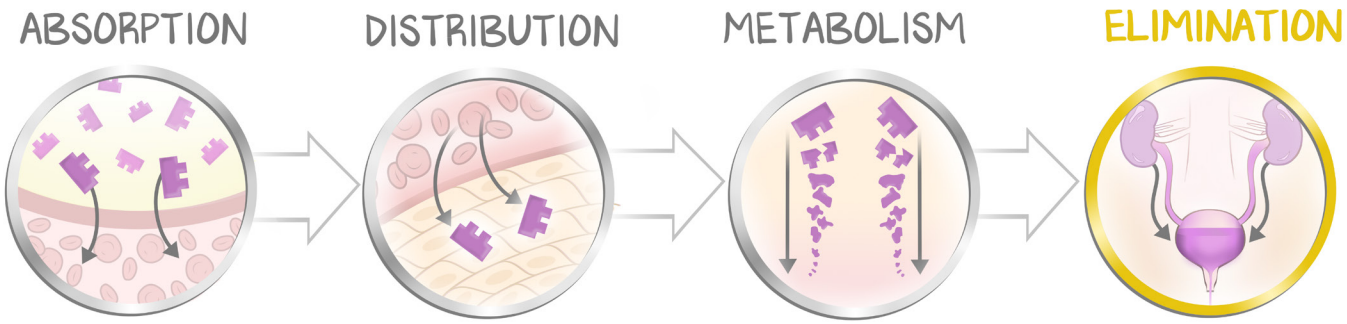

Figure 5.1: Pharmacodynamic Map, Elimination

We learned in the last lesson (Gen Pharm #4: *Metabolism/Biotransformation*) that metabolism means "make the thing more water soluble." The **reason why** we wanted to make things more water soluble through metabolism was so that the drug our body was trying to rid itself of would **get trapped in the urine**—which is water. And the kidney receives 20% of the circulating volume, a **massively redundant volume** if all it did were keep our electrolytes in check. It's redundant intentionally so that any toxin (aka drug) is more quickly eliminated.

While drugs can be excreted through sweat and stool, this lesson assumes that **the kidney does all the eliminating**. I cannot emphasize how hard this concept is for 80% of medical students, including myself. The words "clearance" and "elimination" are often used interchangeably to mean "getting drugs out of the body." In this lesson we will be using clearance and elimination in their mathematical representations—they are equations. However, rather than being asked to memorize the equations and then being given some values to simply plug-and-chug, what we help you do is what the test will ask you to do—conceptually utilize clearance and elimination even if the equations themselves elude you.

Clearance

Clearance is a measurement of the volume of plasma from which a substance is completely removed per unit time.

Urinary clearance is specifically assessing the clearance achieved by the kidneys. Inulin is a drug that is freely filtered, is not absorbed by the nephron, and is not secreted by the nephron. That means that if we were to measure inulin's clearance, we would have a direct measurement of the filtration rate at the glomerulus, the **glomerular filtration rate** (GFR). Inulin is fairly unique in these features and its only use is to calculate the GFR using the clearance equation in experiments (or on the test). Most drugs are NOT freely filtered (the next paragraph). Most drugs have a variable rate of absorption or secretion as well. When one of these drugs is circulating in plasma, some of it will be filtered, some may be secreted, and some may be absorbed. The final amount of drug in the urine is the urinary clearance of the drug.

Clearence = Filtered – Secreted + Absorbed

As we learned in #3: *Distribution*, real-life drugs are **protein bound**. If protein bound, the drug is attached to albumin and is too big to be filtered through the glomerular endothelium. That means for most drugs which are not freely filtered, the filtration is **not the GFR**, but a fraction of the GFR, called the **free fraction** of the drug. Only the free fraction not bound to albumin in the plasma gets filtered. In #3: *Distribution* we said the more free drug not bound to albumin there is, the greater distribution into tissue it has. Yep—it distributes into the target tissue. That same feature that allowed the drug to distribute into the target tissue is the same feature that will cause it to distribute through the endothelium into the glomerulus. "Distribution" into the glomerulus puts in the in the compartment that will lead to its elimination.

So what we have is a **GFR** (usually given to us in a vignette by the clearance of inulin), allowing us to determine a **theoretical clearance** based on the free fraction of a drug and GFR, and then a **calculated clearance** based on measurements we do on the plasma concentration and the urine concentration. If what ends up in the urine (the calculated clearance) is larger than the theoretical, then the drug was secreted in addition to being filtered. If what ends up in the urine (the calculated clearance) is smaller than theoretical, then the drug was absorbed. You should not be asked to calculate clearance, but rather respond to it.

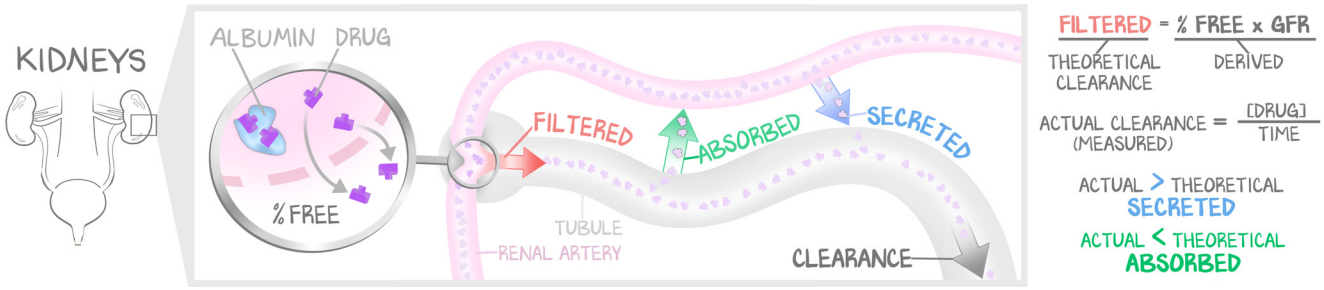

Figure 5.2: Clearance
The kidneys filter a drug in to the tubules, but only the free fraction is filtered, the rest remaining bound to albumin. The kidneys can either secrete or absorb the drug. (c) If what is collected in the urine is more than the theoretical clearance, the drug was net secreted, and if the what was collected in the urine is less than the theoretical clearance, the drug was net absorbed.

Half-Life, First-Order Kinetics, Second-Order Kinetics

The half-life, called $\mathbf{T_{1/2}}$, is how much **time it takes** to **remove half** of the drug from the body. It's a value of **time**. It can be inferred from graphs (see the next section). Notice I used the word "remove" and not "eliminate." From this point forward, elimination is a mathematical number, not the concept of getting rid of a drug.

In humans, the **rate of removal of a drug** is **elimination**. Elimination is expressed differently according to the drug's kinetics. Either there **are enough enzymes** (**first-order kinetics**) to accommodate more drug to be eliminated or there **are NOT enough enzymes** (**zero-order kinetics**) to accommodate more drug.

In Biochemistry, when there were "not enough enzymes" we said that the system was maximized because all the enzymes were **saturated**. When an enzyme becomes saturated, it doesn't matter how much substrate you have; the rate of reaction is already maximized, so adding more substrate won't do anything. If there were unsaturated enzymes, adding more substrate would make the rate of reaction go faster. Now, in Pharmacology, "enzymes" is instead "process of elimination," and "substrate" is "drug."

If the body's process of elimination **is saturated**, then elimination of the drug follows **zero-order kinetics**. This means that the **half-life is variable**. If there's 80 mg of a drug, and the rate at which it can be removed is 20 mg/hour, it would take two hours to get to half of 80 (which is 40). The rate of elimination is still 20 mg/hour, so it would take only one hour to get to half again (which is 20). The time it takes to remove half of the drug changed from two hours to one hour. But the **amount** removed per hour stayed the same. That's zero-order kinetic. Let me point out the key words: **saturated** process of elimination, **zero-order** kinetics, **AMOUNT** of drug.

If the body's process of elimination is **not saturated**, then elimination of the drug follows **first-order kinetics**. In this case, by adding more drug, the body is able to use more resources, and remove more that drug more quickly. Because adding more drug to the body increases its rate of removal, first-order kinetics remove a **certain percentage of drug per hour**. First-order kinetics has a **constant half-life**. If we start with 80 mg and a half-life of one hour, after **one hour** the dose remaining will be half that (40). In another hour, it will be half of 40 (20). And so on and so on. Let me point out the key words: **unsaturated** enzymes, **first-order** kinetics, **PERCENTAGE** of drug.

Zero-order kinetics can be said to remove drugs at a fixed **amount** per hour and to have a **variable half-life**.

First-order kinetics can be said to remove drugs at a fixed **percent** per hour and to have a **fixed half-life**.

The real point to all of this is that drugs that operate under zero-order kinetics **will continue to build to toxic levels and the human body won't be able to increase elimination**, whereas drugs on first-order kinetics will be able to clear more drug as more is added. **Most drugs follow first-order kinetics**. **Alcohol does not**.

Saying the Same Thing in Graphs of Kinetics

If the foregoing is already familiar, go ahead and skip this next section. The last section was done conceptually; this section is done with graphs. To get this right, you must first be able to tell which graph you are looking at, and the test may try to trick you. Graphs of kinetics can be based either on **concentration vs. time** or **log-concentration vs. time**. The first step is to look at the y-axis. If the y-axis is increasing incrementally, and there is equal distance between the increments, you have a regular graph. If the y-axis is increasing incrementally, but there is shorter and shorter distance between the values, you are on a log graph.

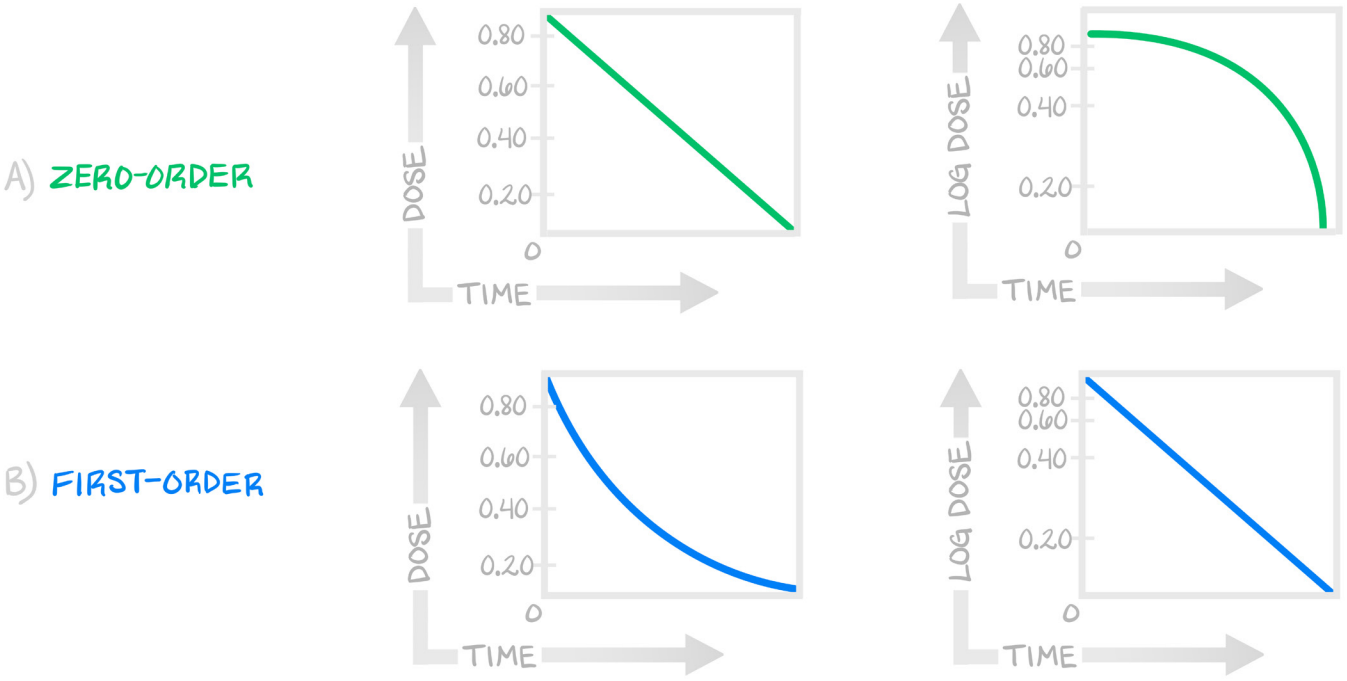

Figure 5.3: Kinetics Graphs
(a) Zero-order kinetics has a constant slope on a regular graph, and a concave curve on a log graph. (b) First-order kinetics has a constant slope on log graph, and convex curve on regular graph.

Zero-order kinetics plots a **flat line** on a **regular graph**, and a **concave curve** (concave means bows out from the x-y axis intersection) on a **log graph**. That is what I remember because it makes the most sense without math (without the log part), and I can extrapolate from there. Because flat-line-**regular**-graph-**zero**-order immediately implies flat-line-**log**-graph-**first**-order.

First-order kinetics plots a **flat line** on a **log graph**, and a **convex curve** (convex means bends down toward the y-x-axis intersection and to the left) on a **regular graph**. That right there is why we're spending so much time on it. Not because it's hard, but because you can be tricked into the wrong answer by looking only at the shape of the line. Having a flat line is not enough. If the line is straight, you need to look at the y-axis to check if it is log or regular.

Zero-order kinetics plots a constant slope on a **regular graph** or goes **concave** on a log graph.

First-order kinetics plots a constant slope on a **log graph** or goes **convex** on a regular graph.

Mathematical Representation of Elimination

Elimination, the mathematical concept, is represented by the letter K. Elimination is the **slope of the line** we just talked about when the line is straight. The line "is straight" when we are looking at a regular graph and zero-order kinetics OR a log graph with first-order kinetics.

Get ready for how easy this is, considering how complicated the last two pages were. When the **slope is steeper**, the K **is higher**, which is the same thing as saying that when the **elimination is faster**, then the drug is **removed faster**.

And

If the drug is removed faster (elimination is higher, *K* is larger, slope is steeper), the time it takes to reach half its concentration (the $T_{1/2}$) is going to be **shorter**.

We have a mathematical way of proving the next statement, but don't do math; just know this equation.

$T_{1/2} = 0.7/K$

It means that there's a relationship between the slope-of-the-line-of-removing-a-drug and the time-it-takes-to-remove-the-drug. It says the same thing that we've been saying all along. If the elimination (*K*) goes up, the half-life goes down (bigger denominator), whereas if elimination (*K*) goes down, the denominator is smaller, so the value of the half-life is larger.

Said in English: if the rate of removal of a thing goes up, the thing will be removed faster.

Said in Math: if elimination (K) increases, the $T_{1/2}$ will decrease.

Putting It All Together—Clearance, Elimination, Half-Life, Volume of Distribution

Clearance = Elimination × Volume of Distribution. Cl = *K* × Vd. How? Why? Where'd that come from? JUST MEMORIZE IT. We just said, "abstract concept equals abstract concept multiplied by an abstract concept." But this is why this lesson is so long.

$$Cl = K \times Vd \quad \text{and} \quad K = \frac{0.7}{T_{1/2}} \quad \text{therefore } Cl = \frac{Vd \times T_{1/2}}{0.7}$$

Clearance is directly related to Vd	Clearance is inversely related to $T_{1/2}$
Clearance is directly related to *K*	*K* is inversely related to $T_{1/2}$
If ↑ *K*, then ↑ Cl and ↓ $T_{1/2}$	If ↑ $T_{1/2}$ then ↓ *K*, and if ↓ *K* then ↓ Cl
If ↓ *K*, then ↓ Cl and ↑ $T_{1/2}$	If ↓ $T_{1/2}$ then ↑ *K*, and if ↑ *K* then ↑ Cl
Clearance and elimination are not the same, but they have the same relationship to $T_{1/2}$ for first-order kinetics.	

Table 5.1: Putting It All Together

Steady State and Maintenance Dosing

Drugs that are eliminated by **zero-order kinetics never reach steady state** because they have a variable half-life. A fixed **amount** of drug is eliminated per time. The concept of steady state requires the elimination of a fixed **percentage** of drug per time. If more drug is given before the previous dose is eliminated, it will accumulate. This is how people get drunk and why people die of alcohol poisoning. Alcohol is zero-order.

Since almost all drugs are eliminated by first-order kinetics, steady state can be achieved. A steady state is achieved when the addition of a dose effectively does not change the concentration in plasma—elimination is balanced with the administration of the dose. The sole determinant of how long it takes to reach steady state is the half-life of the drug. Alterations of the half-life (impaired or induced metabolism or clearance) will alter the steady state.

Give a single dose. The dose will peak at C_{max}, then be eliminated. If a second dose is given prior to complete elimination of the first dose, the total concentration will be whatever was left over from the first plus the new added concentration of the second. If this is continued for multiple administrations, the concentration in the plasma continues to rise. However, since these drugs are being cleared by first-order kinetics, 50% of whatever the concentration is right now is being cleared. With more and more doses, the average plasma concentration tends to level off. There are still peaks and troughs (the highest concentration after administration, the lowest concentration right before the next dose), but the curve begins to oscillate around the average plasma concentration of steady state, named C_{ss}.

Drugs eliminated by **first-order kinetics** take **3.3 half-lives to reach 90% of steady state** and 4–5 half-lives to nearly complete steady state, and **after 7 half-lives** the dosing is said to have **reached steady-state concentration**. After 7 doses, the medication being given at a given dose will have achieved steady-state concentrations. That means that whatever effect we see in the patient after 7 doses is the effect the medication will have. We aren't discussing dosing intervals, but for this discussion, let's assume we are giving the doses at the right time.

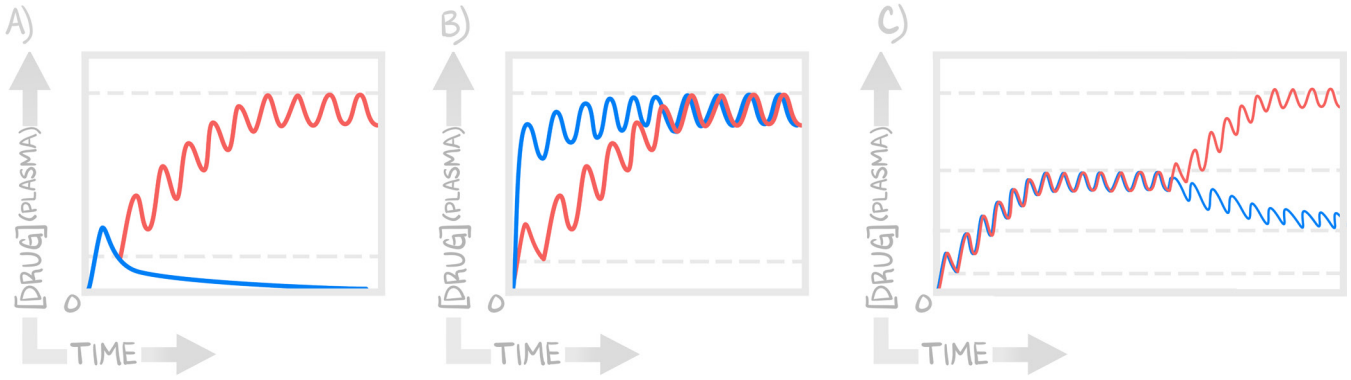

Figure 5.4: Steady State and Pitfalls
(a) Comparison of a single-dose administration curve with peak C_{max} and elimination versus repeated dosings. There are still peaks and valleys, but the average plasma concentration approaches steady state. (b) Effect of a loading dose to achieve therapeutic effect faster, but still steady state is not achieved until after 7 half-lives. (c) Effect of changing the dose. After a change, either an increase or decrease, it still takes 7 half-lives to ensure the new steady-state concentration.

Some pitfalls students commonly run into regarding steady-state concentrations:

First pitfall, what happens when there is a **loading dose**. An **initial larger dose** (a loading dose) does **NOT reach steady state faster**, and does NOT increase the steady-state concentration. But an initial larger dose (whether it's higher in mg or the route of administration increases plasma levels more) will cause a higher initial peak. That initial peak can be used to **achieve a clinically effective dose faster**. With a **loading dose**, even though the peak is higher, and even though removal will be faster, we can reach clinical effectiveness faster. We choose our scheduled dose to reach an effective concentration once steady state is reached. Until it reaches steady state, it is below our desired effective concentration. Rather than waiting for the dose to build up over 7 half-lives, we can give an initial large dose. A loading dose gets us to the effective concentration faster. Giving a mega loading dose gets us to a toxic concentration. So the loading dose, while larger than the regular dose, cannot be as big as you want, just big enough to get the desired concentration

Second pitfall: what happens when the dose is increased? A **bigger chronic dose** reaches steady state in the same number of half-lives as a smaller dose. But a larger dose means a **larger steady-state concentration**. This can be demonstrated in the clinical application of titrating blood pressure medications. We decide on a starting dose (don't worry about how we choose the starting dose), have the

patient take that medication, then bring that patient back into clinic after two weeks. We assess their blood pressure and determine whether more medication is needed. If the blood pressure is not where we want it to be, we titrate the medication up, then have the patient return in two weeks. Two weeks is well after the 7 half-lives required to reach steady state of their new dose (medications dosed daily take about 7 days to achieve steady state; medications dosed twice daily take about 4). We ensure the patient has reached steady-state concentration to assess the therapeutic effect.

Steady State and Real Life

We said above that only factors that influence half-life impact steady state. That assumes the patient is taking the medication the way it is prescribed. We are going to approach steady state again, only using the tub model.

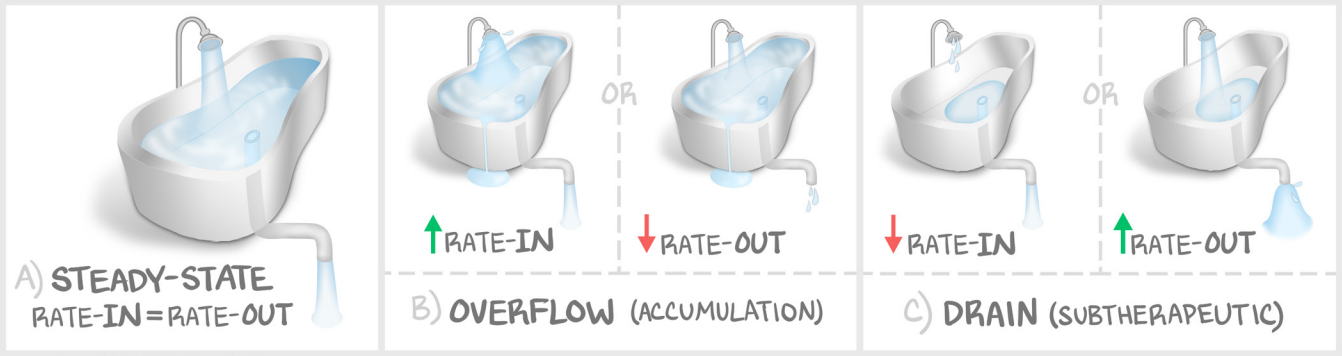

Figure 5.5: One Compartment Model
A tub will reach a steady state if the drain's capacity matches that of the faucet. The "water in" is the faucet. The "water out" is the drain. Alterations in the faucet will cause the water level in the tub to rise or fall, as can alterations in the drain. The level of the water represents the current dose in the plasma. Steady state is a combination of the incoming doses and half-life. In this lesson we are assuming half-life is related to renal elimination only to keep things simple. If the scales tip in either direction, the drug falls out of steady state. (a) Shows the steady state. (b) Shows overflow, either increased in or decreased out. (c) Shower drain, either decreased in or increased out.

First using the tub, since everyone has used, or at least seen, a tub. The starting position is the image in Figure 5.4. The faucet is on, and the drain is open. You've managed to match the rate of water in to exactly the water out by having the faucet turned on at half maximum, and you've placed the drain plug without sealing it shut. You can both increase and decrease the rate of the faucet. You can both plug the drain more (decreasing draining of the tub) and release the plug (increasing the draining of the tub). But right now, even though water is coming in, and water is being drained, the water level in the tub is the same. This is steady state. Now let's tip the scales in either direction. After each example, mentally return the tub back to its steady state.

1. Make no change to the drain and turn the faucet completely off. What happens to the tub? It drains. Water out remains the same, but water in is less, so the water out wins. Mentally reset the tub back to steady state.

2. Make no change to the drain and turn the faucet on maximum. What happens to the tub? It fills. Water out remains the same, but water in is more, so the water in wins. Mentally reset the tub back to steady state.

3. Make no change to the faucet, and fully plug the drain. What happens to the tub? It fills. The water in didn't change, but the water out went to zero, so the water in wins. Mentally reset the tub back to steady state.

4. Make no change to the faucet and open the drain entirely. What happens to the tub? It drains. Water in didn't change, but water out increased, so the water out wins.

Now let's translate the tub to humans. "Water in" is the taking of medications. "Water out" is renal elimination.

1. What is this first item, "turning the faucet off," in a human? If a patient misses a dose or two, **input goes to 0**, but **output remains the same**. It'll still take **many half-lives** to completely remove that drug—about 7 to get rid of it "all." (50%, 25%, 12.5%, 6.25%, 3.125% 1.6%, 0.8%). This will cause a subtherapeutic level, and the drug effect will be lost.

2. What is "turning the faucet on higher" in a human? A higher dose. Taking too much medication. Either the steady state dose increases to match, or there if done acutely, a loading dose at steady state may push the concentration in the blood to toxic levels.

3. What is "plugging the drain in the tub," in a human? Plugging the drain means loss of elimination. For example, a patient gets an acute kidney injury (that they are unaware of) and they remain faithful to their pre-injury regimen, the **input stays the same** while the **output goes down**, leading to an accumulation of the drug. This can reach toxic levels.

4. What is "opening the drain" in a human? Hard to do without first having some pathology. But using the acute kidney injury example, if someone were recovering from renal failure, and they were prescribed a reduced, renally-dosed adjusted dose, as their renal function returns that lower-than-normal dose may no longer be effective.

A medication for the treatment of pulmonary embolism, an anticoagulation medication called enoxaparin, demonstrates renal injury and response to medication dosing very well. Enoxaparin is dosed at 1 mg/kg twice a day for normal kidney function, and once a day with renal impairment. If the patient suffered acute kidney injury and the dose was left at twice a day, the patient could develop life threatening hemorrhage. Enoxaparin is dosed at 1mg/kg once a day if there is renal impairment. If the renally adjusted dose were administered after the kidney injury resolved, the patient would spend half the day without anticoagulation, and is at risk for extending the clot. This example is using the kidney as the only source of elimination, a one compartment model. At the same time, biotransformation in the liver reduces the amount of enoxaparin (turning it into something else), while the kidney is clearing the enoxaparin.